REMARKS

Claims 4-8 are pending. Claim 9 is new. The subject matter in Claim 9 is supported in the specification and original and amended claims. Claims 1-3 have been cancelled as drawn to non-elected inventions. Amendment of the claims and the addition of Claim 9 does not affect inventorship.

Claim Rejections – 35 USC § 112, second paragraph

Claims 4-8 are rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 4, step (b): The Examiner states that it is not clear whether generating the probability table means calculating the probability of appearance of a given residue in the given sequence or the probability of appearance of various residues in a given position of a protein. The Examiner's assumption that this term of art refers to the latter is correct.

As is clearly stated in the specification starting on page 28, starting with the third paragraph:

> "...the probability distribution can be used to generate information entropy scores for each position, as a measure of the mutational frequency observed in the library...In this embodiment, the frequency of each amino acid residue at each variable position in the list is identified...That is, as above, these variable positions are collected and all possible combinations are generated, but the amino acid residues that "fill" the secondary library are utilized on a frequency basis...As will be appreciated by those in the art and outlined herein, probability distribution tables can be generated in a variety of ways...a preferred method of generating a probability distribution table is through the use of sequence alignment programs. In addition, the probability table can be obtained by a combination of sequence alignments and computational approaches. For example, one can add amino acids found in the alignment of homologous sequences to the result of the computation."

The expression "probability distribution" is well known in the art and is explained in the specification on page 28, along with many references that utilize probability distribution (see specification, page 29 among other places)

The Examiner also states that the relation of step (b) to subsequent method steps is not clear in how generating the table affects the next method step.

The claims have been amended to more clearly link step (b) and the additional steps.

B. Claim 4, step (c): The Examiner states that it is not clear which "said amino acid residues" are being combined.

Step (c) has been amended to clarify the antecedent basis of the term "said amino acid residues".

C. Claim 4, step (d): The Examiner states that it is not clear how the process of "ranking" a library generates another library.

Step (d) has been amended to clarify this step.

D. Claim 7: The Examiner states that the term "mutation" lacks antecedent basis. Figure 1 of the specification illustrates the concept that is recited in Claim 7. The claim has been amended for clarification purposes.

Claim Rejections – 35 USC § 101/112, first paragraph

4. Claims 4-8 are rejected under 35 USC 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility. The Office Action asserts that no specific or well-established utility has been disclosed. Reconsideration under 37 CFR 1.111 is requested.

The claims of the present invention provide a method for computationally screening variant protein sequence libraries to generate secondary libraries of useful variant protein sequences, which when synthesized find use in a wide variety of applications, ranging from industrial to pharmacological uses. Furthermore, the methodology of the present invention allows for the rapid screening of large numbers of potential variant sequences for useful variants and the selection of proteins with useful properties. Greater diversity of protein sequences may be obtained by the method of the present invention. See Specification at page 2, lines 13-19; page 4, lines 31-36; page 6, lines 3-8; and page 6, lines 9-17.

The Applicants respectfully draw the Examiner's attention to the Utility Guidelines: In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101. As the CCPA stated in In re Langer:

"As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."

Thus, Langer and subsequent cases direct the Patent Office to presume that a statement of utility made by an applicant is true. For obvious reasons of efficiency and in deference to an applicant's understanding of his or her invention, when a statement of utility is evaluated, Patent Office personnel should not begin an inquiry by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. This can be done by evaluating the logic of the statements made, taking into consideration any evidence cited by the applicant. If the asserted utility is credible (i.e., believable based on the record or the nature of the invention),

a rejection based on "lack of utility" is not appropriate. Thus, Patent Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical field of the invention or for other general reasons.

Compliance with § 101 is a question of fact. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Patent Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility. To do this, Patent Office personnel must provide evidence sufficient to show that a person of ordinary skill in the art would consider the statement of asserted utility "false". A person of ordinary skill must have the benefit of both facts and reasoning in order to assess the truth of a statement. This means that if the applicant has presented facts that support the reasoning used in asserting a utility, Patent Office personnel must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the applicant's assertion of utility (MPEP §2107.02IIIA). The initial evidentiary standard used during evaluation of this question is a preponderance of the evidence (i.e., the totality of facts and reasoning suggest that it is more likely than not that the statement of the applicant is false). It is respectfully submitted that the Examiner has not met this burden.

See also U.S. Patent Nos. 6,188,965; 6,296,312 (cited by the Examiner in the § 103 rejection); 6,403,312; 6,708,120; 6,792,356; PCT/US98/07254 and PCT/US01/40091. Such methods have been used to generate novel proteins with enhanced properties, see for example, U.S. Patent Nos. 6,682,923; 6,627,186; 6,514,729; and 6,746,853 and USSN 10/141,531. See also, Steed et al, *Science* (2003), 301: 1895-1898, a copy of which is enclosed as Exhibit A; Hayes et al., *PNAS*, 99 (25): 15926-15931, a copy of which is enclosed as Exhibit B; and Luo et al., *Protein Science* (2002), 11: 1218-1226, a copy of which is enclosed as Exhibit C.

In the article "Proteins from Scratch" (DeGrado, *Science* (1997), 278:80-81, a copy of which is enclosed as Exhibit D), biochemistry professor William F. DeGrado of the University of Pennsylvania School of Medicine, a world-renowned expert in protein structure, folding and design, comments on the computational platform designed by Dahiyat and Mayo in Science (1997), 278:82-87. This platform is an earlier version of the computational platform that has evolved and is claimed herein. Dr. DeGrado states:

> "Not long ago, it seemed inconceivable that proteins could be designed from scratch. Because each protein sequence has an astronomical number of potential confirmations, it appears that only an experimentalist with the evolutionary life span of Mother Nature could design a sequence capable of folding into a single, well-defined three dimensional structure. But now on page 82 of this issue, Dahiyat and Mayo describe a new approach that makes de novo protein design as easy as running a computer."

Dr. DeGrado further states (col 1, paragraph 3):

"Thus, the problem of de novo protein design reduced to two steps: selecting a desired tertiary structure and finding a sequence that would stabilize this fold. Dahiyat and Mayo have now mastered the second step with spectacular success. They have distilled the rules, insights and paradigms gleaned from two decades of experiments into a single computational algorithm...Thus the rules of ...computational methods for de novo design may now be sufficiently defined to allow the engineering of a variety of proteins."

Further, in 2002, Dr. Jeffery G. Saven, a well-known expert in protein design, has recently published a review of the state of the art in combinatorial protein libraries (see, Saven, JG, Curr. Op. Struct. Biol. (2002), 12:453-458, a copy of which is enclosed as Exhibit E, where he states at page 456, col. 1, 3rd paragraph, lines 6 – 13:

> "Not only can combinatorial methods be used for discovery but also, more deeply, they can inform our understanding of protein properties by generating and assaying whole ensembles of sequences. Traditionally, advances in structural biology have come from examining the structures of naturally occurring proteins, but with combinatorial experiments, an enormous diversity of sequences can be generated at the control of the researcher".

The Saven publication, while not prior art in the instant application, shows that it is known in the art that combinatorial library generation has "real world use". Thus, the discussions above regarding examples of actual utility by Applicant, as well as recognition to those skilled in the art of protein design and combinatorial library generation, meets the utility requirement under 35 USC § 101.

Applicant also respectfully points out that its technology, PROTEIN DESIGN AUTOMATION® (PDA®), has been used successfully with several partners. See the press releases attached as Exhibit F. These partners have found that the use of PDA® technology has "real world" uses to generate novel proteins.

Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong," even when there may be reason to believe that the assertion is not entirely accurate. Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility.

Thus, the burden is shifted to the Examiner. The Examiner analogizes a library to a composition of matter, which has to undergo screening to isolate and identify a product, citing Brenner v. Manson, 148 USPQ 689 (1966) ("Brenner").

Applicants are specifically claiming a **method** of generating a secondary library, not a "library" per se, nor a composition of matter in the instant application. The invention is directed to the method, not the specific nature of the output. Thus, the analogy to Brenner that the Examiner makes is not analogous to the claims in the instant application.
In addition, Applicants respectfully disagree with the analogy to Brenner because the protein variants to be screened by the method of the present invention, synthesized and/or tested find utility in their respective fields. For example, for purposes of the present invention, it does not matter what the class of proteins are. The method of the claimed invention, screens for useful variants having desired protein characteristics. See for example, Specification at page 4, lines 25-30 and page 34, lines 22 to page 35, line 12. For example, the variants produced from the method of the present invention may find use as therapeutic proteins. See Specification beginning at page 34, lines 22, ending on page 35, line 12.

Thus, the burden is shifted to the Examiner. The Examiner analogizes a library to a composition of matter, which has to undergo screening to isolate and identify a product, citing Brenner v. Manson, 148 USPQ 689 (1966). Applicants respectfully disagree because the invention as claimed is in fact a method for generating libraries. Although the Examiner describes the secondary libraries as presently undefined, the method for generating them is fully enabled by the specification and the claims are so directed to such method, not the particular composition of the library. The library generated will necessarily vary with the particular target protein identified, as well as the use of the different parameters of the method.

It is submitted that the present invention has utility under §101 and Applicants respectfully request that the rejection be withdrawn.

5. Claims 4-8 are also rejected under 35 USC § 112, first paragraph since the claimed invention is not supported by either a specific asserted utility or a well established utility.

The arguments made above with respect to 35 USC §101 are equally applicable to the rejection under 35 USC §112, first paragraph. The techniques described in the recited methods have a specific and well-established utility, and one skilled in the art would know how to use the claimed invention, particularly as demonstrated in the patents and scientific articles discussed above.

Claim Rejections – 35 USC § 103

6. Claims 4-8 are rejected under 35 USC USC § 103 as being obvious over Srinivasan (US Patent 5,884,230) or Srinivasan et al. (Biomacromolecules) in view of Altshul and Levitt and Lacroix et al (US 2002/0072864) and further in view of Mayo et al (US 6,269,312).

As a preliminary matter, none of the cited references teach comparing multiple sequences of or using an alignment program to create calculated or modeled sequences to

then generate a probability distribution. In other words, the probability distribution is generated from modeled or calculated sequences in Applicant's invention. Nor do any of the references suggest or teach a method of determining the "fitness" of the library sequences identified, nor do they suggest or teach a means to determine whether such modified proteins are relatively "better" or "worse" than the original target protein. Applicant's claimed method is designed to create either broader diversity or focused diversity in a variant protein library to allow for more efficient and productive screening than is possible with just an alignment program or just a probability distribution.

Srinivasan (US Patent 5,884,230) (the '230 patent)

The '230 patent teaches a protein modeling system that utilizes a 3 dimensional structure of a template protein and a sequence alignment between the template protein and the protein to be modeled that uses relative positional information between the pairs of amino acids of the template and modeled protein.

The Examiner states that "Srinavasan et al describe method of protein modeling which generates sequence of a model protein using alignment program, identifies three-dimensional structure of the model protein, geometrical constraints required to maintain the structure, and then populates the three-dimensional space with amino, which are either original residues of the model protein or their equivalents (see cols. 4-5)." Applicant respectfully submits that the method described by Srinavasan does not generate a sequence of a model protein. Rather, a pre-existing sequence is merely aligned with a homologous sequence, in order to facilitate the generation of a modeled structure for the protein in question. Furthermore, Srinavasan teaches the population of 3D space with atoms, based on their topological equivalence in the two proteins. The method in general is teaching the modeling of pre-existing (and fixed) protein sequences in order to determine their three-dimensional shape.

Finally, there is no suggestion, teaching or disclosure of modeled protein structures or sequences that differ from the known, pre-existing sequences; nor does it teach the generation of a primary, secondary or tertiary library of variant proteins; nor does it teach or suggest the combination of a sequence aligned primary library with a residue probability distribution step, then a ranking step; and finally there is no disclosure, teaching or suggestion of synthesizing members of a secondary library. That is, the '230 patent never suggests testing the variant sequences generated to determine if they are better than wild-type.

Srinivasan et al. (Biomacromolecules) ("Srinivasan et al.")

This publication discloses homology modeling to build 3 dimensional structural models where there is a high degree of sequence identity between a given known crystal

structure template and a protein with unknown folding structure. The publication compares homologous differences derived from the template with a database of dimeric building blocks derived from loop regions of high-resolution crystal structures.

The Examiner states "Similarly, the same authors describe homology guided protein design in "Biomacromolecules, 1997, wherein the replacing residues were selected from either those known to be conserved in the family of proteins (at the bottom of 76 of the reference) – i.e., having high probability to be in a given location – or, by similar mimetics (see page 77 of the reference). Applicants respectfully submit that the referenced paragraphs are discussing the correlation between sequence and structural changes observed in the naturally occurring protein sequences of CD40L, TNF, and Fas ligand. The publication is actually discussing the substitutions that nature has made (e.g. "at position 255 in CD40 ligand a Ser is substituted for a conserved Phe"). The authors are merely discussing substitutions of one naturally occurring protein relative to another, and there is no suggestion by the authors of using such substitutions to engineer any of the proteins to generate non-naturally occurring sequences. On p. 77, the authors discuss the use of an Ile zipper trimer protein to guide the trimerization of CD40L. Applicants submit that the construction of a fusion protein is not relevant to the instant claims.

While Applicant may use a 3 dimensional structure (or a homologously generated structure), i.e., scaffold protein, as a starting point to generate libraries according to the claimed method, Srinivasan et al., do not use an alignment program to generate modeled proteins, from which a probability distribution is made (based on the modeled proteins, not the naturally occurring ones). Nor does Srinivasan even generate libraries, let alone secondary or tertiary libraries in this publication. Srinivasan et al. is only trying to determine folding in a protein where the structure is not known using naturally occurring proteins. But in order for the Srinivasan et al. technique to work, there must be a similar protein that has a crystal structure available and which also has a high degree of sequence similarity.

Further, there no suggestion, teaching or disclosure to use an alignment program to generated modeled proteins, and from such modeled protein library, the generation of a probability distribution of amino acids in a protein.

Altshul

Altshul teaches a gapped BLAST and a Psi-BLAST program that can be used to identify gapped alignments. The reference also discloses methods for combining statistically significant alignments generated by BLAST into a position-specific score matrix. Thus, Atschul is not teaching the use of a probability distribution of amino acids at residues of modeled proteins as is specifically recited in Applicant's claims.

Moreover, Atschul does not suggest, teach or disclose generation of a modeled secondary library from a modeled primary library, where at least one sequence of the

secondary library differs from the first; Further, Atschul does not specifically rank any secondary library sequences; Nor is there any teaching, suggestion or disclosure to synthesize any secondary or tertiary sequences.

Levitt (1978)

Levitt discloses a probability distribution technique that analyzes the assignment of secondary structure to provide the frequency of occurrence of the 20 naturally occurring amino acids in an α helix, a β sheet and reverse-turn secondary structure. Levitt weighs the occurrences in different structures to eliminate redundancies while still providing frequencies that are integrated into a probability distribution of those frequencies.

Levitt merely teaches a probability distribution technique, not the methodology recited by Applicant. Again, Levitt is not generating probability distribution from a library of modeled proteins. Levitt does not suggest, teach or disclose generating a primary library of sequences by use of an alignment program, then generating a probability distribution of a library of secondary sequences that differs from the primary library. Nor does Levitt suggest or teach synthesizing some of these secondary library sequences.

Lacroix et al (US 2002/0072864)

It is noted that Lacroix et al., have an effective filing date less than 7 months before the effective date of the instant application.

Lacroix et al. teach a computational modeling technique virtually identical but less comprehensive than the earlier described Mayo et al, discussed below. Lacroix et al., teach a method for choosing a set of amino acid positions in a target protein by identifying at least one substitute for each amino acid position in the set; determining at least one conformer for each substitute, substituting coordinates of each conformer for the coordinates of the positions in the target protein; minimizing the value of a calculated solution score by adjusting the geometry of the conformer to obtain a "solution structure"; and determining whether the "solution structure" has a score that is lower than a threshold value.

Lacroix et al. do not disclose all of the steps of Applicant's methodology. There is no suggestion, teaching or disclosure of using an alignment program to generate a primary library of modeled sequences, then generating a probability distribution to create a second modeled library of the modeled primary library sequences. When Lacroix et al refer to a "library", Lacroix et al mean a set of rotamers to be substituted at a particular amino acid position. LaCroix et al is looking for **a** solution structure, not a library of structures. LaCroix et al does not even suggest generation of secondary libraries, merely the generation of a solution structure after applying an energy scoring function to a set of rotamers at a particular amino acid position in the target protein. Moreover, Lacroix et al never suggests or teaches synthesizing the "solution structure" that they generate.

Mayo et al. (US 6,269,312)

Applicant respectfully submits that the Examiner's recitation of what Mayo et al discloses relates to the generation of a primary library, not a secondary or tertiary library. This is only one step of Applicant's claimed method. Mayo et al. do not specifically disclose or consider sequence alignment. In addition, Mayo et al do not use sequence alignment, then a probability distribution to generate a secondary library, nor a further ranking step to generate a tertiary library. This combination, as recited in the instant claims, provides either broader diversity or a more focused diversity of the library generated. There is no suggestion of secondary or tertiary library generation in the '312 patent.

Combination of Srinivasan (US Patent 5,884,230) or Srinivasan et al. (Biomacromolecules) in view of Altshul and Levitt and Lacroix et al (US 2002/0072864) and further in view of Mayo et al (US 6,269,312)

None of the cited references alone or in combination teach or make obvious Applicant's invention as recited in claims 4-9.

To establish a *prima facie* case of obviousness, three basic criteria must be met: 1) suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify or combine reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference must teach or suggest all the claim limitations. (See MPEP §2142).

With respect to the first criterion, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify or combine reference teachings. Each of the references teaches one or maybe two steps of Applicant's methodology. The Applicant respectfully points out that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention"; see *In re* Fine, 5 USPQ2d 1596 (Fed. Cir. 1988). Applicant is not claiming alignment programs, probability distribution or synthesizing proteins *per se,* but the generation of a secondary library by first generating a modeled primary library using an alignment program, then generating probability distribution of the modeled primary library to generate a modeled secondary library that differs from the primary library. This technique is designed to create either broader diversity or focused diversity in the variant protein library to allow for more efficient and productive screening than is possible with just an alignment program or just a probability distribution.

Further, while the Examiner states that synthesizing a library of proteins is obvious, none of the references cited do such synthesis. Again, Applicant is not claiming synthesis techniques *per se*, but synthesis of at least a portion of the secondary library of sequences by these techniques. These techniques are defined only in the context of Applicant's defined method, not a synthesis *per se*. Applicant has recited claims that are directed to further diversifying the secondary library by use of the various synthesis techniques described in claims 5-8.

None of these references suggest or disclose the concept of combining computational techniques to generate additional diverse libraries in a sequential step-wise fashion. Therefore, the first prong of the analysis has not been met.

The second criterion, a reasonable expectation of success, has been demonstrated in several working examples have been included in the application as filed. Additional support for the expectation of success may be found in the publications and press releases discussed above with respect to the §101 rejection.

Finally, the prior art reference must teach or suggest all the claim limitations. As discussed above, none of the six prior art references teaches or suggests all the claim limitations of the present invention.

Applicants respectfully submit, in light of the foregoing discussion, none of the references, either alone or in combination, supports a finding that a *prima facie* case of obviousness has been established against the present invention.

Double Patenting

Claims 4-8 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-8 of US Patent 4,403,312.

The Examiner states that while the claims are not identical as the '312 claims do not utilize an alignment program, "this will be an alternative approach obvious to an artisan; in addition, the specification clearly identifies use of alignment software". However, as the Federal Circuit has repeatedly stated, it is the claims that are considered in double patenting, not the specification. See for example, *Panduit Corp. v. Dennison Mfg. Co.*, 1 USPQ 2d 1593 (Fed. Cir. 1987); *Ortho Pharmaceutical Corp. v. Smith*, 22 USPQ 2d 1119 (Fed. Cir. 1992), etc. Thus this rejection is improper and should be withdrawn.

Claims 12, 21-24 (Applicant assumes the Examiner means Claims 4-8) are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-29 of co-pending application no. 09/927790.

Applicant respectfully requests that the claim scope be reevaluated once the claims of both applications are in condition for allowance.

The Examiner is invited to contact the undersigned at (415) 781-1989 if any issues may be resolved in that manner.

Dated: 4/25/05

Respectfully submitted,
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Filed under 37 C.F.R. § 1.34(a)

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